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Review

Treatments to Promote Neural Repair after Stroke

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Stroke remains a major cause of human disability worldwide. In parallel with advances in acute stroke interventions, new therapies are under development that target restorative processes. Such therapies have a treatment time window measured in days, weeks, or longer and so have the advantage that they may be accessible by a majority of patients. Several categories of restorative therapy have been studied and are reviewed herein, including drugs, growth factors, monoclonal antibodies, activity-related therapies including telerehabilitation, and a host of devices such as those related to brain stimulation or robotics. Many patients with stroke do not receive acute stroke therapies or receive them and do not derive benefit, often surviving for years thereafter. Therapies based on neural repair hold the promise of providing additional treatment options to a majority of patients with stroke.

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Introduction

Neural repair can be defined as restoring the structure or function of the central nervous system (CNS) after injury such as stroke. Numerous categories of repair-based therapies are under study. Therapies based on repair are distinct from those based on prevention and from those that aim to reduce acute injury such as reperfusion or neuroprotection.

Repair-based therapies typically have a treatment time window measured in days-weeks or longer and so have the potential to be accessed by a large fraction of patients with stroke, including those with hemorrhagic stroke. This is a potential advantage for reducing the high burden of disability after stroke. In middle- and high-income countries around the world, stroke is the leading neurological cause of lost disability-adjusted life years.[1] Each year, 795,000 people in the United States experience a symptomatic stroke. An estimated 6,600,000 Americans adults have had a symptomatic stroke, with a prevalence that increases with age, and 13,000,000 people in the United States have had a silent stroke[2] that while clinically inapparent at onset might nonetheless impact long-term function. The mean survival after stroke is 6 to 7 years, with approximately 85% of patients living past the first year of stroke.[3] Thus, the majority of patients with stroke survive the acute episode and live with enduring disability for years to come.

Current acute stroke interventions reduce disability in only a limited fraction of patients. The only drug approved to treat acute stroke in the United States remains tissue plasminogen activator (tPA),[4,5] which many patients do not receive[6,7] largely due to its narrow treatment time window. A recent estimate is that approximately 5% of patients with stroke in the United States receive tPA acutely post-stroke.[7] Importantly, half or more of those receiving intravenous tPA acutely post-stroke have significant long-term disability.[4,5] An even small fraction of patients with acute stroke receive acute endovascular reperfusion therapies,[8] although recent positive trials in this field are stimulating research into increasing the rate with which these interventions are given. Repair-based therapies complement acute therapies

not only in terms of different biological targets but also in terms of treatment time window, measured in days to weeks or longer, and so have the potential to help a large proportion of patients affected by stroke.

Spontaneous repair after stroke

Neural repair after stroke arises spontaneously after stroke and continues for many weeks, possibly for years for some behaviors particularly language and cognition. Understanding spontaneous repair provides insights useful for treatment-related repair, a point that is underscored by the fact that treatments promoting repair are often provided in the context of spontaneous repair.

Stroke triggers several molecular cascades that produce injury, inflammation, or spontaneous repair.[9] Animal studies have provided insights into stroke-induced recovery mechanisms. These are summarized here, but detailed reviews can be found elsewhere.[10-17] An experimental stroke alters expression of numerous genes,[13] leading to increases in levels of key growth factors,[18,19] growth of synapses and dendrites,[20,21] axonal remodeling and angiogenesis,[22-25] and enhanced brain excitability mediated by alterations in glutamate and gamma-aminobutyric acid (GABA) receptor subtypes.[26-29] These events are often concentrated in perilesional tissue but are not confined there; indeed, spontaneous growth-related changes following a unilateral infact arise broadly, within the contralesional hemispheres,[20,30,31] in ipsilesional areas connected to the lesioned area,[32] and even downstream in the spinal cord.[33]

Brain responses to a new unilateral stroke can be organized into three broad temporal epochs (Figure 1). The first epoch occurs during the initial hours after stroke onset and represents an opportunity to salvage threatened tissue, e.g., via reperfusion or neuroprotection. The second epoch commences days to weeks following stroke and corresponds to the peak weeks of spontaneous neural repair. Mechanisms of spontaneous recovery are most robust during this time.[34] There are numerous specific time windows within this epoch which vary according to the gene or molecule of interest and which correspond to specific treatment time windows for treatment-induced neural repair after stroke.[13,35] The third epoch represents a chronic phase whereby the brain is relatively stable with regards to endogenous repair-related events, but modifications in brain structure and function are still possible with specific interventions. These three epochs delineate distinct biological states and have clinical implications with regards to delivery of restorative therapies.

Studies of spontaneous neural repair after stroke in human subjects generally rely on non-invasive methods, in comparison with the direct tissue-based measures employed in preclinical investigations. The most commonly used methods include structural and functional magnetic resonance imaging, positron emission tomography, single photon emission computed tomography, electroencephalography, magnetoencephalography, transcranial magnetic stimulation (TMS), and near infrared spectroscopy; these provide a systems-level perspective on neural repair.[34] These studies show anatomical changes such as thickened or thinned cortex in brain regions remote from stroke injury.[36-39] Other studies have focused on functional changes, reporting

Acute injury

- This phase is measured in hours and varies according to features of injury.
- The key therapeutic strategy here is to reduce the extent of injury.
- Main treatment approaches examined to date include
  - ▶ reperfusion
  - ▶ neuroprotection

Recovery stage

- This phase of spectacular growth begins shortly after acute injury has stimulated restorative processes, evolves over several weeks, and varies in relation to factors such gene expression, molecular milieu, environment, and experience.
- This key therapeutic strategy here is to enhance the processes underlying spontaneous recovery. Other targets may be related to modifying inflammation, lifting diaschisis, or reducing late neuronal death. Acute injury is fixed and so its reduction is not a strategy during this stage.
- Main treatment approaches examined to date include
  - ▶ growth factors
  - ▶ monoclonal antibodies
  - ▶ drugs
  - ▶ cell-based therapies
  - ▶ activity-based therapies
  - ▶ brain stimulation

Chronic state

- This phase begins once spontaneous behavioral recovery has reached a plateau and the recovery stage critical period has ended. This phase typically occurs by three months post-strokes for the motor system, sometimes later in cognitive and language domains, and continues for the lifetime of the stroke survivor.
- This key therapeutic strategy here consists of interventions to induce a state of enhanced plasticity, given that the biological state of spontaneous recovery has receded.
- Main treatment approaches examined to date include
  - ▶ drugs
  - ▶ cell-based therapies
  - ▶ activity-based therapies
  - ▶ brain stimulation

Figure 1. The brain progresses through three epochs after stroke. Each has a distinct biology defined by multiple processes ongoing in parallel. For each epoch, the general time scale, key therapeutic strategies, and main treatment approaches studied in preclinical and human studies are summarized.

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modulation in local and distant cortical and subcortical activity, changes in interactions between hemispheres, shifts in cortical representational maps, and alterations in brain connectivity.[34,40-42] These modulations in brain structure and function after stroke are of greatest benefit to patients with more severe injury[43-48] and at times can be detrimental when present in patients with milder injury. The exact contribution that such findings make to behavioral recovery can be difficult to estimate across the human stroke population, where there are numerous sources of heterogeneity such as pre-stroke behavioral status, site and size of stroke-related brain injury, and choice of therapies following stroke. In general, return of functional anatomy towards normal patterns is associated with better behaioral outcomes.[49]

Therapies to promote neural repair after stroke

Numerous categories of post-stroke restorative therapy are under study,[15,50-52] many in human trials. Most focus on a single agent or intervention, and with further understanding of monotherapies, combination therapies are likely to receive increased attention. As above, some restorative therapies are introduced within days of stroke onset and so interact with spontaneous neural repair mechanisms, and others are initiated months to years after stroke onset.

Growth factors

Growth factors have high potential as an approach to neural repair because they are important during normal CNS development and because they play a key role in spontaneous neural repair through mechanisms that include angiogenesis, cell proliferation and differentiation, migration, survival and apoptosis, synaptic plasticity, and immunomodulation.[53,54] In some cases, a rich clinical experience exists for growth factors outside of stroke indications, such as for patients with renal failure or infertility. The utility of growth factors to promote stroke recovery has been studied in preclinical stroke studies. In many cases, preclinical studies suggest that administration of exogenous growth factors 24 hours or more following stroke onset provides a significant long-term benefit on behavioral outcomes. Examples of growth factors studied in the preclinical setting include brain-derived neurotrophic factor (BDNF),[55] epidermal growth factor plus erythropoietin,[56] and human chorionic gonadotropin (hCG) plus erythropoietin.[57]

Data in humans are more sparse regarding growth factor therapy after stroke as an approach to neural repair. Most trials to date have examined hematopoetic growth factors, which have a long record of safety in human applications. Granulocyte-colony stimulating factor (G-CSF) is one such growth factor that was evaluated in the AX200 for Ischemic Stroke (AXIS) study,[58] which found that G-CSF given within 12 hours of stroke was safe and well-tolerated in 44 patients. A separate study of 60 patients also found G-CSF to be safe after stroke.[59] However, a follow-up study, the AXIS-2 study,[60] compared the middle G-CSF dose from the AXIS study (135 μg/kg) with placebo in 328 patients within 9 hours of stroke onset, using a multi-center, randomized, placebo-controlled study design. These authors found that G-CSF was not different from placebo on the primary endpoint, modified Rankin scale score at day 90. A meta-analysis of studies introducing G-CSF days to years post-stroke did not find favorable effects.[61]

Erythropoietin has also been studied to promote neural repair. Preclinical studies suggest that systemically administered erythropoietin enters the brain and improves when delivered as a sole agent after acute injury is fixed, e.g., 24 after stroke onset.[62] Erythropoietin was also found to be safe in a randomized, placebo-controlled study of 167 patients who received two doses of erythropoietin versus placebo beginning 48 hours after stroke.[63] Other studies found favorable effects of sequential growth factor administration, giving a separate growth factor (epidermal growth factor[56] or beta-hCG[57]) prior to erythropoietin, with the entire regimen initiated 1 to 7 days post-stroke, possibly by promoting neural stem cell proliferation.

The sequential growth factor approach was translated to humans in the Beta-hCG+Erythropoietin in Acute Stroke (BETAS) study, a single-dose, multisite, open-label, non-controlled safety trial that gave 3 hCG doses beginning 1 to 2 days post-stroke followed by 3 erythropoietin doses beginning 7 to 8 days after stroke. This study identified no safety concerns, and eight of 12 patients had a day-90 Barthel index score ≥95/100.[64] The BETAS study was followed by the REGENESIS study.[65] This was intended to be a randomized, placebo-controlled, double-blind proof of concept study of sequential hCG (385 μg subcutaneous on day 1, 3, and 5 of study participation) and erythropoietin (30,000 IU intravenous on day 7, 8, and 9) using the BETAS study treatment schedule. This trial was put on hold by regulatory authorities due to concerns related to an acute stroke neuroprotective trial[66] in which high dose erythropoietin (40,000 IU IV at <6, 24, and 48 hours; cumulative dose 120,000 IU over <48 hours) was initiated within 6 hours of stroke onset, despite widely different time windows, and thus biological states in the CNS, as compared to REGENESIS: erythropoietin was initiated within 6 hours of stroke onset in the acute neuroprotective trial and 7 to 8 days after stroke onset in the REGENESIS trial. In that acute trial,[66] high dose erythropoietin was associated with significantly increased mortality relative to placebo, mainly intracerebral hemorrhage

within the first week post-stroke, which was largely attributable to an interaction between erythropoietin and tPA co-administration—indeed 63% of enrollees in that study received thrombolytic therapy. Subsequently, the REGENESIS trial was modified to be a dose-ranging safety study and, due to financial constraints, largely moved to India. Enrollment was terminated by the sponsor early after 96 enrollees. In REGENESIS, sequential hCG+erythropoietin growth factor therapy was found to be safe; however, treatment groups did not differ in the primary endpoint, National Institutes of Health Stroke Scale (NIHSS) score change to day 90. However, it is uncertain whether study hypotheses were robustly tested in this trial, for example, 18% of subjects dropped out, 31% of enrollees had mulitiple assessors on the primary outcome measure over time despite pretrial training to use a single examiner, and only 23% of patients received even a single session of occupational therapy.

Growth factors are generally large proteins for which CNS ingress is limited. A number of strategies have been proposed to overcome this, such as helping growth factors to cross the blood-brain barrier via conjugation to a molecular Trojan horse.[67] Another strategy has been to transfect an exogenous stem cell with a gene encoding for a growth factor, as has been studied for fibroblast growth factor-2,[68] glial cell line-derived neurotrophic factor,[69] BDNF,[70] vascular endothelial growth factor,[71] placenta growth factor,[72] or hepatocyte growth factor.[73] Development of small ligands is another potential solution.[74-76] Even if one assumes growth factor access to the CNS is limited after stroke, these molecules can nevertheless influence brain plasticity through extraneural targets, e.g., via the immune system.[77,78]

Monoclonal antibodies

The ability of other large biological molecules, such as monoclonal antibodies, to promote neural repair has also been evaluated. Monoclonal antibodies modulate activity within targeted signaling pathways by binding to specific targets such as receptors or cell surface markers. This approach has revolutionized patient care in numerous conditions, including neoplastic, immunological, and others. In the context of neural repair after stroke, monoclonocal antibodies have been used to neutralize molecules that inhibit growth in the CNS, with the overall appraoch being to produce a more permissive growth environment. Axonal growth has long been known to occur in the peripheral nervous system;[79] however, in the CNS three major inhibitors (myelin-associated glycoprotein [MAG], oligo-myelin glycoprotein, and Nogo-A) reduce the extent to which the growth environment is permissive, a situation that is exacerbated by the increase of these molecules following stroke onset.[13,80] Use of a monoclonal antibody to block these inhibitory molecules promotes axonal growth.[81,82] One recent study randomized 42 patients with stroke to placebo versus one of three doses of intravenous GSK249320, a humanized IgG1 monoclonal antibody to MAG that has a disabled Fc region. Each patient received two infusions: the first administered 24 to 72 hours after stroke onset, and the second, 9 days later. No safety concerns were identified,[83] and one of the secondary endpoints, gait velocity, showed a trend toward improvement with GSK249320 compared with placebo. However, a subsequent phase IIb double-blind, randomized, placebo-controlled study that enrolled 134 patients with ischemic stroke 24 to 72 hours prior found that two doses of the antibody was not superior to placebo for improving gait velocity.[84] The antibody was well tolerated and showed low immunogenicity, findings that are potentially useful to future studies aiming to use a monoclonal antibody to modify activity in specific biological pathways to improve recovery from stroke.

Drugs

Numerous small molecules have also been examined to improve outcome after stroke. Small molecules may have advantages in terms of transport through the blood-brain barrier, with many being nonpolar and small in size,[85] and thus often have high access to the brain. In many cases, candidate small molecules represent repurposed drugs, i.e., those already approved for other indications. Many of the small molecules studied for neural repair target a specific brain neurotransmitter system.

Monoaminergic drugs have been studied most often. An early focus for the field was on amphetamine,[86] which acts on multiple monoaminergic targets. The initial human experience in small trials was favorable,[87,88] but the Subacute Therapy with Amphetamine and Rehabilitation for Stroke (STARS) study was not. This randomized, double-blind, placebo-controlled trial did not demonstrate a benefit.[89] The authors examined 5 weeks of twice-weekly amphetamine coupled with physiotherapy versus placebo coupled with physiotherapy in 71 patients enrolled 5 to 10 days post-stroke. The drug was safe but did not improve the primary outcome, motor recovery over 3 months using the arm/leg Fugl-Meyer motor score, as compared to placebo.[89] Strengths of this study include the use of a single therapist to administer all physiotherapy, use of a single examiner to assess study outcomes, which reduces variance and increases study power, and coupling drug exposure with training. A weakness of the study is that the treatment protocol was not directly translated from preclinical findings, and so the optimal dose, timing, and frequency of amphetamine to promote stroke recovery remains uncertain. It is difficult to determine whether STARS showed that amphetamine is not useful overall, or simply that the one protocol examined (twice weekly amphetamine beginning 5 to 10

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days post-stroke) is not useful.

The neurotransmitter dopamine regulates many aspects of neural functioning including excitability, synaptic transmission, plasticity, protein trafficking, and gene transcription.[90] Not surprisingly, therefore, dopamine has a major role in numerous diverse brain processes such as movement, reward, learning, and plasticity.[91] Furthermore, the role of dopamine in motor control is well established, with dopaminergic terminals in motor cortex contributing to cortical plasticity and playing a critical role in motor skill learning.[92,93]

Drugs that boost dopaminergic neurotransmission can improve learning and plasticity in healthy subjects.[94] Similar results have been reported after stroke. A randomized, double-blind, placebo-controlled study in 53 patients within 6 months of stroke onset found that 3 weeks of 100 mg of levodopa (in combination with a decarboxylase inhibitor, carbidopa, given once/day and combined with physical therapy) was significantly better than placebo combined with physical therapy on the primary endpoint, motor status by the Rivermead Motor Assessment after 3 weeks.[95] This study awaits replication. Dopaminergic drugs have the potential advantage that measures of genetic variability may help predict inter-subject differences in treatment response.[96,97] Smaller studies using other dopamine agonists have been largely negative, e.g., a placebo-controlled, double-blind study of 33 patients 1 to 12 months post-stroke did not find a difference between a 9-week course of ropinirole+physiotherapy compared to placebo+physiotherapy on gait velocity.[98] Small studies hint at the potential for noradrenergic drugs.[99-101] Larger, well designed, fully powered trials are needed in this promising area of research.

Serotonin, another monoaminergic neurotransmitter, may also be helpful for promoting neural repair and improving stroke recovery. Serotonin normally plays a role in modulating multiple brain functions, particularly cognitive functions such as response inhibition and memory consolidation, and this neurotransmitter also modulates the impact of punishment-related signals on learning and emotion.[102-104] Earlier reports supported the potential utility of selective serotonin reuptake inhibitor (SSRI) drugs for improving motor outcomes after stroke.[105-108] Recent reports remain supporting, suggesting that boosting serotonin neurotransmission improves stroke recovery. Robinson et al.[109] performed a multisite, randomized controlled trial for prevention of depression among 176 non-depressed patients enrolled within 3 months of stroke onset. Patients randomized to the placebo arm were significantly (P<0.001) more likely to reach the primary outcome, development of major or minor depression, as compared to patients in either of the two active comparator arms, which were (1) the SSRI escitalopram or (2) problem-solving therapy. One analysis of a subgroup of these patients found that cognitive outcomes at 12 months were significantly better among those randomized to escitalopram, independent of depression, while a separate subgroup analysis found a lower incidence of generalized anxiety disorder with escitalopram or with problem-solving therapy.[110]

The strongest evidence in support of an SSRI to improve outcomes after stroke comes from The Fluoxetine for Motor Recovery After Acute Ischemic Stroke (FLAME) study.[111] This was a double-blind, placebo-controlled trial that enrolled non-depressed hemiplegic/hemiparetic patients 5 to 10 days after onset of ischemic stroke. Patients were randomized to 3 months of oral fluoxetine (20 mg/day) versus placebo. Those randomized to fluoxetine showed significantly greater gains on the primary endpoint, change in the arm/leg Fugl-Meyer motor score from baseline to day 90 (P=0.003), a remarkable 9.7 point difference between treatment arms on this 100 point scale, though this result must be interpreted in light of the fact that a small, non-significant difference in baseline scores favored the SSRI-treated group. Phase 3 trials are underway to further evaluate this finding. Measures of genetic variability may inform likelihood of response to a serotonergic drugs.[112,113]

Kim et al.[114] randomized 478 patients in Korea with recent (<21 days) ischemic or hemorrhagic stroke to oral escitalopram (10 mg/day) or placebo for 3 months. Patients with a history of severe depression were excluded. At baseline, enrollees overall had mild strokes (average baseline NIHSS score of 4.8) and mild depression (Montgomery-Åsberg Depression Rating Scale score 10.7), with approximately one-fourths showing moderate or severe depressive symptoms. While the drug was well tolerated, the frequency of the primary endpiont, moderate or severe depressive symptoms after 3 months defined as Montgomery-Asberg Depression Rating Scale ≥16, was not different between the two treatment arms. A shift analysis did find a significant benefit of escitalopram, mainly due to a reduced number of patients with mild depressive symptoms at 3 months (P=0.044), and the drug also significantly reduced anger symptoms. *Post hoc* analysis found that the number of patients with zero or minimal depressive symptoms at 3 months was significantly higher in the escitalopram group, suggesting directions for endpoint selection for future trials of SSRI after stroke. A measure of motor function at 3 months also did not differ between treatment groups, in response to which the authors speculate that SSRIs might improve motor dysfunction after acute stroke only in patients lacking early depression.

Norepinephrine transmission as a drug target has received limited study to date in the context of stroke recovery. Normally, noradrenergic neurotransmission broadly amplifies neuronal activity, increases the general level of excitability, and selectively

amplifies activities evoked by unexpected inputs.[115] This effect of norepinephrine on regulating overall arousal levels has a modulatory effect on executive function.[103] To date there has been only a handful of studies of noradrenergic drugs to promote stroke recovery. These have been small in size but showed promising results.[100,116,117]

Drugs that modulate neurotransmission in acetylcholinergic pathways have also received limited study in relation to neural repair. Acetylcholine inputs to neocortex are important to procedural memory and operant conditioning.[118] Acetylcholine enables plasticity by selectively amplifying anticipated inputs and weakening non-anticipated inputs.[115] Modulation of nicotinic cholinergic neurotransmission alters attention, while muscarinic cholinergic receptors play a greater role in cognitive flexibility.[103] Luria[119] long ago advocated for cholinergic therapies as a major pathway to enhancing recovery after brain damage. Studies in rodents[120,121] and primates[122] with experimental stroke support this view, but data from human subjects with stroke remain sparse,[123] though preliminary studies have been favorable.[124,125] Data with respect to non-motor aspects of stroke recovery are limited in quantity but potentially promising,[123,124,126] and a recent study in 33 patients found that donepezil to be safe when initiated within 24 hours of stroke onset.[124]

Other small molecules have been studied. Evidence suggests potential utility of drugs that modulate GABA[28] or glutamate[27,127] receptors, and these effects may be particularly dependent on the time post-stroke when the agent is introduced. Sildenafil is a phosphodiesterase type 5 inhibitor that has shown promise as a restorative agent post-stroke[128,129] and has been tested in human subjects recovering from stroke.[130]

Cell-based therapies

Cell-based therapies are receiving increased attention, with many types of cell-based therapy under study.[131,132] Examples include transformed tumor cells, adult stem cells such as marrow stromal cells, umbilical cord cells, placental cells, embryonic stem cells, fetal stem cells, and induced pluripotent cells. Cells may be administered alone or with a bioscaffold, with genes modified, or after exposure to particular culture conditions such as low oxygen or neurotrophin exposure. Stem cells may be autologous, allogeneic, or xenografts.

Considerable attention has been drawn to mesenchymal stromal cells (MSCs), which are an adult non-hematopoietic pluripotent cell. Abundant preclinical evidence suggests that MSCs improve behavioral outcomes after experimental stroke via several different mechanisms in parallel,[133] a potential advantage over pharmacological therapies that act via a single treatment mechanism,[134-136] and with a time window that is measured in days or weeks post-stroke. A meta-analysis examined 46 preclinical studies in which MSC was given after cerebral ischemia.[137] MSC improved outcomes in 44 of the 46 studies. The mean effect size for MSC administration was consistently very large, e.g., averaging 1.78 for the modified Neurological Severity Score across 28 studies; results were similar overall when analyses were restricted to studies that initiated MSC ≥24 hours after stroke onset. Early phase clinical studies to date are promising.[138-142]

Cellular therapies can introduce challenges that are uncommon with other classes of restorative therapy. For example, such therapies are not a drug or a device but instead consist of living cells. As such, the biological potency and identity of the therapy can change over time, e.g., during storage or shipping. Some stem cells can persist for months or even years after administration and so require prolonged periods of assessment after implantation. Certain cells generate ethical concerns among some patients and scientists.[143]

Activity-based therapies

A number of intensive activity-based therapy regimens have been studied, targeting motor deficits, aphasia, and other forms of impairment after stroke. For example, constraint-induced movement therapy trains the affected limb while restraining the non-affected limb in order to overcome learned disuse of the affected limb. In the Extremity Constraint Induced Therapy Evaluation (EXCITE) trial, constraint-induced therapy was associated with significant gains in motor outcome in 222 patients enrolled 3 to 9 months after stroke onset,[144] with these effects remaining significant for years.[145] This approach has also been studied in patients with aphasia.[146] The timing of intensive therapies is important. The Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS) trial examined constraint-induced movement therapy early after stroke. Among 52 patients enrolled within 1 month of stroke onset, higher intensity of therapy was associated with poorer behavioral outcome at day 90[147]—a very high dose of activity too early after stroke might be net harmful. The Locomotor Experience Applied Post-Stroke (LEAPS) trial compared two therapies focused on gait in 408 patients within 2 months of stroke, and found that treadmill training with body-weight support did not differ from progressive exercise at home managed by a physical therapist in effects on walking ability 1 year after stroke.[148] Importantly, the LEAPS trial found that a majority of patients with stroke can experience significant behavioral gains when therapy is initiated many weeks after stroke onset, with 52% of treated patients showing improved gait velocity 1 year after stroke onset. Two recent trials compared different activity-related therapy in the subacute[149] or chronic[150] phase after stroke and did not see a difference in

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treatment gains in relation to dose of therapy. One interpretation of these two findings is that the doses studied, 30[149] or 32[150] hours of activity-based intervention, were too low and that very high doses of activity-based therapy may be key to improving patient function, similar to the need for very high amounts of motor practice to show substantial improvement in motor skills among healthy persons.

Robotic and telehealth devices

The effect of therapy delivered by robotic devices has also been examined. Numerous robotic devices have been studied.[151-155] These devices offer potential advantages, such as consistent and long-lasting output, programmability, utility for virtual reality applications, safety, high precision, the potential for an improved therapist:patient ratio, and great potential for telerehabilitation and therefore ability to reach underserved regions.[156] However, concerns exist with some aspects of robot-based intervention, for example, the need to understand the mechanism of action, the response of the therapist community to a robotic device, the response of patients to reduced interaction with a human therapist, the effect of such devices on task ecology and object affordance, the limited repertoire that fixed devices have, and the nature of the measurements that a robot is programmed to report.

In one of the largest studies of robot therapy after stroke, Lo et al.[157] enrolled 127 patients in the chronic phase of stroke and found that robot-assisted therapy did not significantly improve motor function after 12 weeks, as compared with usual care or intensive therapy; in secondary analyses, robot-assisted therapy improved outcomes over 36 weeks as compared with usual care but not with intensive therapy. This study may be complicated by the fact that enrollees had relatively severe motor deficits.

Robotic devices have great promise but further research is needed. One recent review noted that (1) effects on motor control are small and specific to the joints targeted by the robotic intervention; (2) limited data support generalization of robot-derived gains to broader functions; and (3) little data exist among patients in the initial weeks following stroke onset.[155] Factors that might represent avenues for improving the impact of robotic therapy include more fully defining the relationship between robotic therapy and traditional physiotherapy, and matching the right patients with the right robotic devices and protocols.

Telehealth approaches are receiving increased attention due to their ability to provide high doses of therapy in a simple, efficient, and accessible manner that can extend the resources clinicians can provide to stroke survivors.[158] There are many different approaches under study, targeting various neurological deficits, using divergent methods to drive patient behavior, and in some cases combining rehabilitation and prevention strategies via the same system.[159-163] We recently evaluated a home-based telerehabilitation system in patients with chronic hemiparetic stroke with onset 3 to 24 months prior and stable arm motor deficits.[164] Enrollees received 28 days of telerehabilitation using a system delivered to their home, with each day consisting of one structured hour focused on individualized exercises and games, stroke education, plus an hour of free play. Compliance was excellent: participants engaged in therapy on 329 of 336 assigned days (97.9%). Arm repetitions across the 28 days averaged 24,607±9,934 per participant. Arm motor status showed significant gains (change in the Fugl-Meyer score of 4.8±3.8 points, P=0.0015), with half of the participants exceeding the minimal clinically important difference. Although scores on tests of computer literacy declined with age (r=–0.92, P<0.0001), neither the motor gains nor the amount of system use varied with computer literacy. Daily stroke education via the telerehabilitation system was associated with a 39% increase in stroke prevention knowledge (P=0.0007). Depression scores obtained in person correlated with scores obtained via the telerehabilitation system 16 days later (r=0.88, P=0.0001). In-person blood pressure values closely matched those obtained via this system (r=0.99, P<0.0001). Based on these findings a phase II trial is underway, the results of which are expected to be announced in 2018.[165]

Brain stimulation

The brain is an electrical organ and expends considerable energy maintaining a specific cellular resting potential. Not surprisingly, therefore, electrical and electromagnetic interventions have the potential to modify brain function and potentially promote neural repair to improve outcomes after stroke. Many forms of brain stimulation have been studied after stroke, including repetitive TMS, theta burst stimulation, epidural cortical stimulation, transcranial direct current stimulation, transcranial alternating current stimulation, and stimulation via a laser-based device.[166] A related intervention, vagal nerve stimulation, has also been evaluated in early phase clinical trials.[167] There is precedence for a focus on brain stimulation, as the gold standard therapy for major depression remains a form of brain stimulation—electroconvulsive therapy,[168] and repetitive TMS has been approved by the U.S. Food and Drug Administration for the treatment of major depression.[169] Some results with brain stimulation to promote improved outcomes after stroke, mainly targeting motor outcomes, have been favorable[170,171] while others have not.[172,173] Large, well designed trials are needed, and further study of non-motor endpoints is also critical. A phase III trial aiming to improve arm motor outcomes in patients with chronic hemiparetic stroke examined neurosurgically implanted epidural cortical

stimulation plus physical therapy but did not find this intervention to be significantly different from physical therapy alone;[174] *post hoc* analysis indicated response to brain stimulation was substantially greater among subjects with preservation of physiological integrity or with subtotal injury to key motor system anatomical structures, suggesting the ability to stratify patients to reduce trial variance and increase effect sizes.[36]

Conclusions

Preclinical studies have suggested a large number of therapies that may have to improve recovery from stroke. These are in various stages of translation, with most at an early point of clinical trials. Principles of promoting neuroplasticity in a clinical setting are emerging and have been reviewed elsewhere.[175-177] Issues unique to stroke recovery and rehabilitation studies are increasingly being recognized[178-180] and are important to effective clinical research in this area. Many patients do not reach the hospital in time to receive interventions that can reverse a stroke, and half of those who do receive such therapies still show significant long-term disability. Restorative therapies that aim to harness clinical neuroplasticity may be accessible by a large fraction of patients with stroke and so hold the promise to reduce deficits and improve function for a majority stroke survivors.

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